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ABSTRACT

By drawing on human biomonitoring data and limited environmental samples together with outputs from the CalTOX multimedia, multipathway source-to-dose model, we characterize cumulative intake of organophosphorous (OP) pesticides in an agricultural region of California. We assemble regional OP pesticide use, environmental sampling, and biological tissue monitoring data for a large and geographically dispersed population cohort of 592 pregnant Latina women in California (the CHAMACOS cohort). We then use CalTOX with regional pesticide usage data to estimate the magnitude and uncertainty of exposure and intake from local sources. We combine model estimates of intake from local sources with food intake based on national residue data to estimate for the CHAMACOS cohort cumulative median OP intake, which corresponds to expected levels of urinary dialkylphosphate (DAP) metabolite excretion for this cohort. From these results we develop premises about relative contributions from different sources and pathways of exposure. We evaluate these premises by comparing the magnitude and variation of DAPs in the CHAMACOS cohort with the whole U.S. population using data from the National Health and Nutrition Evaluation Survey (NHANES). This comparison supports the premise that in both populations diet is the common and dominant exposure pathway. Both the model results and biomarker comparison supports the observation that the CHAMACOS population has a statistically significant higher intake of OP pesticides that appears as an almost constant additional dose among all participants. We attribute the magnitude and small variance of this intake to non-dietary exposure in residences from local sources.

INTRODUCTION

Pesticides are heavily used in the Salinas Valley, a largely agricultural region in Monterey County, California. In 2001, a year for which we have combined use and national/local biomonitoring data, 240,000 kg of organophosphorous (OP) pesticides were applied to or near an area of 2,000 km^2 around the Salinas River water shed on a variety of food crops *(1)*. Intensity of pesticide use varies widely in this area, with OP pesticide application rates up to 350 kg/km^2 (on a regional area basis). The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) project is a prospective cohort study of children's environmental health based in the Salinas Valley that has successfully characterized OP pesticide metabolite levels in maternal urine for a population of pregnant Latina women and their children up to age two *(2,3)*. However, CHAMACOS analysis of specific sources (agricultural use, carry-home occupational exposures, home use, food residue, etc.) that give rise to these metabolite levels is underway. Cumulative intake of pesticides depends on exposures to humans through a set of pathways including ambient air, indoor air, food, water, soil, and house dust. There is not yet sufficient residue concentration data available to construct specific exposure pathway intake (food, ambient air, indoor air, dermal uptake, etc.). For the present, we must rely on models to supplement other exposure data. Population-specific models for residential exposures tend to take a bottom-up approach by aggregating from multiple sources to cumulative dose *(4)*. But here we use a top-down approach by matching indicators of exposure and dose to potential sources using mass balance models.

Monitoring both pesticide use and the pesticide biomarkers in urine in the context of mass-balance exposure models offers an important opportunity to study the fate and impact of pesticides in regions such as the Salinas Valley. OP pesticides have a short half-life in the human body (on the order of hours) and their metabolites have half-lives on the order of days—making them difficult as tools for assessing cumulative exposure without some adjunct modeling analysis. Multimedia, multipathway source-to-dose models provide tools for assessing the distributions of cumulative exposures within a defined population *(5-8)*. But there are few current efforts to systematically evaluate the combined capabilities and limitations of biologic samples and models as integrated tools for interpreting source-to-dose relationships.

In this paper we use both exposure models and biomonitoring data to evaluate the relative contribution of different OP pesticide exposure pathways to pregnant, primarily Latina, women in the Salinas Valley. For this cohort of roughly 600 women and an intensive sampling study of 20 other farm-worker families in the Salinas Valley, we have obtained OP pesticide use, environmental sampling, and biomarker data *(2, 3, 9,10)*. Our assessment framework is illustrated in Figure 1. We adapt the CalTOX multimedia, multipathway pesticide exposure assessment model *(11)* to the Salinas Valley and combine it with the Bennett and Furtaw *(12)* indoor mass balance model and with food residue estimates obtained from the U.S. Food and Drug Administration Total Dietary Survey (TDS) *(13)* to make estimates of the relative magnitude, median range, and variation in OP pesticide intake from multiple sources and through multiple pathways for the CHAMACOS women. From this we estimate cumulative median OP intake for the CHAMACOS cohort and use this intake to estimate expected levels of urinary dialkylphosphate (DAP) metabolite excretion in this cohort. We then compare the magnitude and variation of measured urinary DAP levels in the Salinas population to those in the National Health and Nutrition Evaluation Survey (NHANES) for the same time period *(14)*. Similarities and differences in the magnitude and range of observed DAP excretion as reflected in CHAMACOS and NHANES provide a basis for evaluating OP intake attributable to different sources and pathways. This last step provides a basis to address questions regarding the model-based exposure premises about key sources of exposure:

- Is diet the common and dominant exposure pathway?
- To what extent is the chemical activity (fugacity) of pesticides indoors equal to that outdoors?
- To what extent are regional (Salinas Valley) sources important to cumulative intake?

METHODS

This study requires a number of component methods. Here we describe methods along with important choices and assumptions used to characterize the study region and the study population; develop the conceptual source-to-dose model; select and parameterize both the

regional mass balance model and the indoor mass-balance model, and develop algorithms for inhalation, residential hand-to-mouth, dermal uptake, and dietary intake.

Study Region

CHAMACOS is a community/university partnership investigating environmental pesticide, allergen, and other toxicant exposures to women and children in the Salinas Valley *(2)*. This region is approximately 25 kilometers wide and 110 kilometers long, extending from Castroville in the north to King City in the south. According to the 2000 U.S. Census, the population of the Salinas Valley is 376,668 people, approximately 57% of which are Latino. The temperate climate makes agricultural production possible almost year-round. In 2001, approximately 240,000 kilograms of OP pesticide active ingredient were applied in this area, a level typical of recent years *(1)*. In addition, approximately 5% of study participants reported home use of OP pesticides, although more than 40% used other classes of pesticides in the home *(15)*.

Study Population

The CHAMACOS study population is 94% Mexican or Mexican-American, with 96% of participants living within 200% of the federal poverty line as defined by the U.S. Bureau of Census. Pregnant women were eligible for enrollment in the CHAMACOS study if they entered prenatal care between September 1999 and November 2000 at either of two community clinics in the Salinas Valley (Clinica de Salud del Valle de Salinas and Natividad Medical Center). At enrollment, all participants were at least 18 years of age, eligible for Medi-Cal health insurance, less than 20 weeks gestation, fluent in English or Spanish and planning to deliver their child at Natividad Medical Center. Informed consent was obtained from all study participants following procedures established by the University of California Berkeley Human Subjects Review Board. A complete description of the CHAMACOS study population and methods has been published previously *(2)*.

Pesticide Use Data

California requires 100% reporting of all agricultural, structural and landscape pesticide use. Pesticide use reporting (PUR) data is reported to the California Department of Pesticide Regulation (DPR) and summarized annually by: crop; product (mass of active ingredient is then derived by DPR); location (geocoded to one square mile); date; and pounds applied. We use the PUR data to quantify OP pesticide inputs in the Salinas Valley environment. Table 1 summarizes the combined agricultural, landscape maintenance, structural pest control and roadside pesticide usage of OP pesticides in the region during the period 1999-2001 *(DPR 2000, 2001)*. The *Supporting Information* describes how the PUR data is linked to CalTOX.

Urine collection and DAP metabolite data

Our biomonitoring data is based on spot urine samples collected from women participating in the CHAMACOS study during early pregnancy (~13 weeks gestation [n=592]). As part of the ongoing NHANES, the CDC has reported DAP metabolite levels in spot urine for the U.S. population, stratified by age, sex, and racial/ethnic groups *(17)*. The DAP metabolite concentrations were measured in 1,949 urine samples collected from U.S. residents 6-59 years of age during 1999 and 2000. CHAMACOS spot urine samples were collected according to the procedures outlined by the Centers for Disease Control (CDC) for use in NHANES *(14)* and are described in more detail by Bradman et al. *(3)*. Six non-specific urinary OP metabolites were measured in both populations, three dimethyl DAPs: dimethylphosphate (DMP), dimethyldithiophosphate (DMDTP), and dimethylthiophosphate (DMTP); and three diethyl DAPs: diethylphosphate (DEP), diethyldithiophosphate (DEDTP), and diethylthiophosphate (DETP).

Source-to-Dose Modeling

We modeled five of the most heavily used OP pesticides in the Salinas Valley. Two of these pesticides, chlorpyrifos and diazinon, are metabolized in humans to diethyl DAP metabolites that are excreted in urine and the other three, dimethoate, malathion and oxydemeton-methyl are metabolized to dimethyl DAP metabolites that are excreted in urine. Table 1 shows that for the Salinas Valley in 2001 these five account for 95% of OP pesticides

metabolized to the diethyl DAPs, 85% of the OP pesticides metabolized to the dimethyl DAPs, 89% of the 191,757 kg of OP pesticides that metabolize to any DAP compound, and 71% of the approximately 240,000 kg of total Salinas Valley OP pesticide use *(1)*.

Regional Mass Balance Model

We use the CalTOX multi-media fate and multi-pathway exposure model *(18-20)* to estimate pesticide concentrations in the air, dust, and soil of CHAMACOS participant residences in the Salinas Valley attributable to the PUR data. CalTOX uses a fugacity-based mass balance approach to link PUR emissions to OP concentrations in outdoor air, indoor air, soil, water, etc. Fugacity is a metric for quantifying chemical activity at low concentrations. Fugacity can be viewed as the "escaping tendency" of a chemical in a phase, has dimensions of pressure, and is related to concentration by a proportionality constant. CalTOX (version 4.4ch) is a quasi-dynamic regional-scale multimedia mass-balance model that provides both deterministic and probabilistic outputs *(11, 21)*. CalTOX consists of a fugacity-based multi-media contaminant fate model that links concentrations in the ambient environment to concentrations in media with which the human population has contact (i.e., personal air, tap water, foods, household dusts, etc.). Algorithms to estimate environmental concentrations in the CalTOX model are described in detail elsewhere *(18, 22)*. CalTOX has been widely used for chemical classification and multimedia risk assessments. The *Supporting Information* for this paper provides a summary of the inputs required by CalTOX and the specific chemical properties data for the five OP pesticides as well as the landscape parameters used in CalTOX to characterize the Salinas Valley environment.

Residential Scale Exposure Estimates

We couple the household fate/exposure model developed by Bennett and Furtaw *(12)* with outdoor air and soil concentrations obtained from CalTOX to estimate indoor air, surface, and dust concentrations. Some of these concentrations are measured, but the model results helps explain how these concentrations arise. These concentrations are used to estimate dermal, hand-to-mouth, and inhalation intake of the pregnant women in the CHAMACOS cohort. The Bennett and Furtaw *(12)* model is a fugacity-based dynamic mass-balance compartment that includes air

(both gas phase and aerosols), carpet, smooth flooring, and walls. The Bennett and Furtaw *(12)* model provides fugacity capacities for indoor compartments and mass transfer rate coefficients between compartments in an archetypal residential environment in the Salinas Valley. Bennett and Furtaw *(12)* showed good comparison of their results with measurements of chlorpyrifos in air and carpets from an independent study. *Supporting Information* describes the mass balance processes considered in our residential exposure model and summarizes the indoor mass balance model assumptions and parameter values used in our application of the Bennett and Furtaw *(12)* model to the CHAMACOS cohort. In our approach here, the key output from the indoor mass balance model is the overall residence time (Tov) of each OP pesticide transferred to the indoor environment.

Intake from Non-Dietary Exposure Pathways

We modeled non-dietary exposures through inhalation, non-dietary ingestion, and dermal contact with indoor surfaces. Because we focus on median intake estimates, and because the non-dietary exposures are lower than and less uncertain than the dietary intake, we rely first on approximate models that tend to give reasonable median intake estimates.

For inhalation exposure the intake ($Intake_{inh}$ in nmol/d) is estimated as the product of the daily breathing rate (13 m^3/d from Layton *(23)*) times the time-weighted personal-air concentration:

$$Intake_{inh} = BR \times (C_{air} \times ET_{ao} + C_{inair} \times ET_{ai}) \quad [1]$$

where BR is the daily breathing rate, m^3/d; C_{air} and C_{inair} are, respectively, the pesticide concentration in ambient air and indoor air, nmol/m^3; and ET_{ao} and ET_{ai} are times allocated to outdoor and indoor environments.

The key to characterizing non-dietary ingestion with a fugacity model is recognizing that chemicals are brought to the mouth and transferred to saliva by a number of processes including soil/dust ingestion, mass transfer from air to saliva, and hand-mouth contacts. For non-dietary residential ingestion estimates, we assume that (a) the fugacity indoors is the predictor of non-dietary ingestion, (b) the saliva within the mouth (due to hand-to-mouth actions and simple

solution equilibrium) brings saliva to a steady-state fugacity based on air-to-saliva diffusion and dust ingestion, and (c) the amount of saliva swallowed is equal to that produced. Under these assumptions our mass-balance based estimate of daily non-dietary ingestion intake, $Intake_{ndi}$ in nmol/day is

$$Intake_{ndi} = Ing_{saliva} \times f_{indoor} \times Z_{water} \times \theta_{saliva} \times 10^{-3} \text{ nmol/mol} \quad [2]$$

where Ing_{saliva} is the amount of saliva produced and assumed ingested (0.0015 m^3/d *(24)*); f_{indoor} is the pesticide fugacity in the indoor environment (both in air and dust), Pa; Z_{water} is the fugacity capacity (ratio of equilibrium concentration to fugacity) of saliva (assumed equal to water) in mol/m^3-Pa, and θ_{saliva} is the ratio of the mass-balance-based steady state fugacity in saliva to the fugacity of the indoor environment. This ratio is less than one and is based on the balance between transfers to saliva by diffusion and dust ingestion and losses by swallowing. θ_{saliva} is chemical dependent and has values 0.000045, 0.014, 0.030, 0.17, and 0.29 respectively for oxydemeton methyl, malathion, chlorpyrifos, dimethoate, and diazinon. The *Supporting Information* provides a summary of the method used to obtain our estimates of θ_{saliva}.

The key to characterizing dermal uptake with a fugacity model is recognizing that residential contacts drive the skin toward but not always to the fugacity of the indoor environment, f_{indoor}. The fugacity of the skin surface drives mass transfer through the skin. To set up this mass transfer, we need the fugacity capacity of the stratum corneum, Z_{skin} in mol/(m^3-Pa), which is the product of chemical-specific skin/water partition coefficient K_m in L(water)/kg(skin), Z_{water} in mol/(m^3-Pa), and the ratio of skin density to water density, assumed equal to 1 m^3(water)-kg(skin)/[m^3(skin)-L(water)]. K_m is estimated as 0.64 + 0.25 $K_{ow}^{0.8}$ *(25)*. Based on these assumptions we obtain the estimate of dermal uptake $Uptake_{drm}$ in nmol/d as

$$Uptake_{drm} = f_{indoor}\theta_{skin} Z_{skin}(D_{skin}/\delta_{skin})A_{skin}T_c \times 10^{-3} \text{ nmol/mol} \quad [3]$$

where D_{skin} is the diffusion coefficient in stratum corneum taken to be 5×10^{-14} m^2/s *(25)*; δ_{skin} is the thickness of the skin (~25 μm), A_{skin} is the area of exposure skin (~0.5 m^2), T_c is the effective contact time (6 h = 22,000 s), and θ_{skin} is the ratio of the mass-balance-based steady

state fugacity on expose skin surface to the fugacity of the indoor environment. This ratio is less than one and is based on the balance of pesticide transfers to and from the skin surface by diffusion and surface contacts. θ_{skin} is chemical dependent and has values 0.014, 0.095, 0.14, 0.41, 0.97, and 0.29 respectively for chlorpyrifos, oxydemeton methyl, malathion, diazinon, and dimethoate. The *Supporting Information* provides details on methods used to obtain our estimates θ_{skin}.

Food Residue Exposures

We estimate dietary exposure to our five OP compounds using food residue data from the US Food and Drug Administration (FDA) Total Diet Survey (TDS). The TDS, or "Market Basket Study", is an ongoing FDA program that carries out chemical residue analyses on "table-ready" foods *(13)*. In order to estimate OP intakes and compare them to median levels of urinary metabolites in the NHANES and CHAMACOS women, we multiplied the levels of the OP analytes reported in the TDS diet (version 2) by the food-by-food average reported daily consumption for the US women in the age range 25 to 30 years obtained from the US Department of Agriculture Continuing Survey of Food Intake by Individuals (CFSII) *(13)*. To match the time period of our urine samples, we use TDS data from 1999 through 2001 market baskets. Specifically MB 99-1 through MB 01-1, which have been matched by FDA to consumption data reported in USDA's 1987-88 Nationwide Food Consumption Survey (1987-88 NFCS) *(26, 27)*. We organized our results into cumulative intake in nmol/d of diethyl and dimethyl OP pesticides. We restricted this evaluation to the diethyl OP pesticides chlorpyrifos and diazinon, and the dimethyl OP pesticides dimethoate malathion and oxydemeton methyl. We assume that the diet of CHAMACOS study participants delivers a range of pesticide residue doses similar to the US population as reflected in NHANES. We also assume that these five pesticides reflect the major fraction of OP pesticide use on US food products for the period 1999 to 2001.

From the CFSII we determined the average daily food consumption of 25-30 year old women to be 2080 g/d for 320 separate food items. In the MB data only a small fraction of these items have reported residues for the five OP pesticides considered here. For example over the period 1999-2001 and for the pesticides chlorpyrifos, diazinon, dimethoate, malathion, and

oxydemeton methyl, the percentages of the 2080 g that have a reported residue concentration are, respectively, 3.8%, 0.4%, 1.1%, 8.2%, and 0.1%. For these five pesticides the average residue concentrations in the foods with reported residue levels are respectively 4.4 ppb, 3.5 ppb, 4.4 ppb, 6.8 ppb, 64 ppb—levels that all appear to be just above the detection limit. To address the significant uncertainty associated with the large fraction of foods with no reported residue, we bracket our estimates of food intake with two assumptions. First we obtain a lower bound estimate of pesticide intake through food by considering only foods with detected residue and assuming all other foods have no residue. Then we obtain an upper bound estimate of pesticide intake through food by combining foods with detected residue with all other foods assuming they have a residue concentration that corresponds to value that is just below the apparent LOD. For chlorpyrifos, diazinon, dimethoate, malathion, oxydemeton methyl we have assigned this "non-detected" residue concentrations respective values of 2 ppb, 2 ppb, 2 ppb, 3 ppb, and 2 ppb.

Combined Evaluation of Model Results and Biomonitoring Data

We use the combined CalTOX and Bennett Furtaw model results together with results from non-dietary-residential and dietary exposure estimation methods described above to obtain estimates of the median intake of pesticides for the CHAMACOS population for each metabolite class. We compare metabolite levels found among the 356 women ages 18 to 40 participating in NHANES to levels found in the CHAMACOS population. The 1999-2000 NHANES sample included 96 pregnant women between the ages of 18 and 40 *(17, 28)*. We developed log probability plots of measured DAP concentrations in urine to compare the Salinas and NHANES women and look for significant differences that would help sort out exposures pathways. In our analyses we apply no sample weights to the NHANES data.

RESULTS

We consider three types of results. First the output of the combined CalTOX/indoor environment model including ambient air, soil, indoor air, indoor surfaces and indoor dust concentrations. We provide the CalTOX output in combination with the indoor mass balance model to evaluate dermal and non-dietary ingestion residential exposures. We then report on dietary exposures obtained from the TDS residue data combined with food intake. We then

compare our combined intake estimates to biomarker data for women in both the CHAMACOS and national (NHANES) populations.

Estimates of Outdoor Air, Indoor Air, Indoor Dust and Indoor Surface Concentrations

Based on pesticide use data in Table 1 as input, we obtained for our five candidate pesticides, multimedia estimates of regional average concentrations in ambient air, soil, and water. We assume that when annual average quantities of pesticides are applied, the effective environmental release is half to surface soil and half to air. We ran the CalTOX model in steady state and made probabilistic estimates of environmental concentrations, but we present here the median results. The indoor air model included only transport from ambient air and soil to the indoor environment, no indoor uses were considered. We set the amount of soil tracked into each home at 10 g/d *(29)*. For chlorpyrifos, diazinon, malathion, and dimethoate this parameter is not important because less than 1% of total pesticide mass transported indoors is from soil transport and the rest is by air transport. But for our estimate of total oxydemeton methyl transported indoors, 30% comes in attached to soil. Once indoors our model estimates of the relative mass distributions of chemicals among indoor air, indoor dust, and indoor surfaces (including walls, ceilings, bare floors and carpet) indicates that for all five pesticides the mass distribution is more than 99% on surfaces--particularly vinyl floors and carpets with only trace quantities in air and dust (see Supporting Information for more details).

In Figure 2, we present estimates of environmental media fugacities (both ambient and indoor) for the Salinas Valley obtained from CalTOX and compare them with measurements obtained from an intensive environmental sampling study of 20 farmworker families living in the region *(9)*. For chlorpyrifos and diazinon in surface water we use concentration data collected during the period 2000-2001 by Anderson et al. *(30)*. We use fugacities instead of concentrations, because the fugacity reflects relative chemical potential, has the same units in all media, and shows the extent of chemical equilibrium among the media. We obtain fugacity from concentrations by dividing the concentration by molecular weight and the fugacity capacities listed in Table 2. The top two diagrams in Figure 2 presents for chlorpyrifos and diazinon comparisons of model estimates to measured concentrations obtained from Bradman et al. *(9)*. The bottom diagram in Figure 2 presents for dimethoate, malathion, and oxdemeton methyl

model estimates of fugacities in ambient and indoor compartments. For oxydemeton methyl, we make use of 170 dust samples collected around the time of urine sample collection (M. Harnly, Unpublished data). The 80% confidence interval range and mean of these latter data are plotted for comparison in the bottom chart.

Figure 2 highlights a number of modeling issues. First, we note that for all substances, CalTOX results show that fugacity indoors is close to that in the ambient environment and the Bradman et al. *(9)* data supports this premise for chlorpyrifos and diazinon. This suggests that air transport is the primary mechanism by which these pesticides enter the indoor environment. The Bradman et al. *(9)* study data indicate that for chlorpyrifos dust and surfaces indoors are at somewhat lower fugacity than indoor air, indicating that they have not reached complete equilibrium, whereas for diazinon dust and indoor surfaces indoors are at somewhat higher fugacity than indoor air. But there is wide range of variation in these measurements and significant heterogeneity in the dust and surface samples. The CalTOX results indicate that dust and surfaces are at the same fugacity as indoor air and this CalTOX result is within the range of observations for chlorpyrifos and diazinon *(9)*. From this figure we also see that even though their mass emissions are similar, chlorpyrifos reaches a lower relative fugacity than diazinon. This is apparently due to the higher vapor pressure and shorter overall (multimedia) persistence of chlorpyrifos in the ambient environment. In all three panels of Figure 2, the fugacity levels indicate that indoor concentrations approach chemical equilibrium with outdoor air, not with outdoor soil. This is consistent with the observation that air transport is the main mechanism carrying chemicals to the indoor environment. We also see that for the ambient environment, air, soil and water are close to equilibrium for dimethoate and diazinon, but that soil and surface water are at much lower fugacity than air for chlorpyrifos, malathion, and oxydemeton-methyl.

Cumulative Intake from both Non-dietary and Dietary Pathways

Table 3 provides our model-based estimates of the median intake for both (a) pesticides that devolve to diethyl DAP metabolites and (b) pesticides that devolve to dimethyl DAP metabolites. Here we see the dietary intake dominates over non-dietary intake, but is highly uncertain. For comparison, we list the median cumulative output of diethyl and dimethyl DAP metabolites from the CHAMACOS and NHANES (18 to 40 year-old) women. These are

comparable and set the range, which we must match to confirm that our model is capable of capturing the median exposure range.

Joint evaluation of biomarker data and model outcome

We evaluate both the model results and biomonitoring data in terms of the exposure premises supported by each. In spite of the large amounts of pesticide used in the Salinas Valley, the model results indicate that dietary intake is greater than non-dietary exposures. But when we use the model results to make estimates of OP intake, these results also reveal that regional sources are important contributors to overall intake (Table 3). Thus we turn to biomarker measurements to further explore this premise. Figure 3 presents a probability plot for the distribution of total diethyl and dimethyl DAP concentrations in both the women in the NHANES population (356 samples) and the 592 women selected from the Salinas Valley. When comparing the NHANES data to the CHAMACOS data for pregnant women at their first prenatal visit, we found that the median urinary DAP metabolite levels are clearly higher than the median of the NHANES data for the whole country. But the similarity of variance in these data indicates that exposures in the Salinas women have strong similarities to the U.S. population, an indication that cumulative exposures in both populations are attributable to similar sources, most likely food pathways. But a percentile based comparison reveals that for both diethyl and dimethyl DAP metabolites the location of the curves are statistically different such that the CHAMACOS women have systematically higher concentrations then NHANES women, but the spread or slope of the diethyl and dimethyl metabolite curves are not statistically different.

DISCUSSION

Both the modeling results and biomarker comparisons presented here support the observation that the CHAMACOS population has a statistically significant higher intake of OP pesticides compared to NHANES women. But interestingly, this higher intake shows up as an almost constant additional dose among all participants. So the question that arises is whether the magnitude and small variance of this intake can give insight as to the origin of this apparently local contribution. There are a number of plausible pathway/sources to consider—contributions from local (Salinas Valley) pesticide use, residential uses, occupational exposures to the

participants, and dietary sources unique to this population. However, we expect all but the first of these sources (local) to have significant inter-individual variability, and thus would not show such uniformity in added excretion. Based on our exposure modeling it is both plausible and likely that only non-dietary residential exposure from local sources could have the magnitude and low variance of the added excretion that we observe. Both the model and environmental sample analyses reveal uniformity of the fugacity spatially, temporally, and between indoor and outdoor environments. Based on the model analyses and chemical characteristics of the OP pesticides applied agriculturally in the Salinas Valley, we expect these compounds to persist in the home and ambient environments of study participants, resulting in an ongoing source of human exposure. When we combine the information obtained from model predictions, environmental samples, and biomarker comparisons, the only source of exposure that matches all of these elements with regard to magnitude and variance of the added exposure is the local use of OP pesticides.

In both the biomonitoring data and the exposure modeling results developed for the CHAMACOS and NHANES populations, the similarities and differences in these data/results are important for establishing both the source and magnitude of the contribution from local pesticide use. It is of great interest for our exposure assessment that the curves in Figure 3 showing the variance of DAP metabolite levels in urine are so similar for the two populations and for the two metabolite classes. We interpret these results as follows. In any population, dietary exposures are highly variable. But food supplies are similar across the country so we expect more person-to-person (within) variability and seasonal variability than place-to-place (between) variability. So we expect that any large population selected from any region of the country will look similar to the NHANES results when dietary exposures dominate intake. But how can local pesticide uses in Salinas be responsible for a uniform increase in DAP concentrations in the CHAMACOS population? The similar slopes (variance) of matching DAP curves in Figure 3 seem to indicate that unlike the food intake exposure with its large inter-individual variance, the non-dietary residential exposures are systematically higher among the 592 CHAMACOS subjects. We believe this comes about because local residential exposures are distributed more uniformly in the Salinas population due to the dynamics of pesticides in their ambient and residential environments. The support for this premise is the uniformity of the

fugacities in the ambient and indoor environment across the region (an observation supported by both models and measurements). Further supporting this premise is the model-derived persistence of these compounds in the ambient environment (~20 days) and in the indoor environment (>100 days). These factors support the concept that local exposures would be buffered and more uniformly distributed to the population and more likely to appear as a uniform step increase of intake rather than as an intake that would spread the DAP curves.

There are numerous source-to-dose models proposed, discussed, and applied in the current exposure literature. Selection of a model from this range requires an assessment of what is appropriate for the questions at hand—that is characterizing the key sources of exposure for the CHAMACOS cohort. Our principal concern was the trade-off between empirical probabilistic models [e.g., SHEDS *(4)*, Lifeline *(31)*] that emphasize human activity but provide limited treatment of environmental chemistry and the chemical process-based models [see for example *(5, 7, 27)*] that often lack statistical detail on variation of human activities. For us, the key issue is the extent to which the model results and the biomarker results reveal differences in the CHAMACOS and NHANES populations. For this reason we elected to build on the CalTOX chemical mass-balance framework and add indoor mass balance and food exposure models.

The biggest modeling challenge in this assessment was using the TDS residue data for making exposure assessments due to shortcomings of the TDS data. There are two key issues. First the question of how well only four market baskets collected in four different regions can capture the spatial range and temporal variation of residue data. A second and bigger issue is the large number of foods that have no reported residue and the fact that even foods with reported residue levels are very close to the limit of detection (LOD) for that pesticide.

This study provides insight on an alternative use of models. The exposure assessment field has seen substantial progress in the development of mechanistic models that track the migration of chemicals and behavior of humans in the complex web of processes that determine the magnitude and variation of exposure within a defined population. Because the goal of these models is to make predictions that capture all potentially important processes at work within a system, more and more component processes are added, increasing the level of detail

represented. But here we use models more as tools to evaluate interpretations of measurements rather than for prediction. Even though more detailed models offer greater fidelity, they may be less reliable than simpler models for this type of evaluation. For its study cohort, the CHAMACOS project provides important and detailed exposure information, including excretion of pesticide metabolites; pesticide concentrations in outdoor air, indoor air, dust, and surfaces; dietary information, and activity data. But even with this rich data there are not sufficient degrees of freedom to calibrate complex mechanistic models that can have hundreds of parameters. Even with the CHAMACOS data such models can easily become over-parameterized, with the consequence that they offer little insight, leading to the conclusion that we should make better use of the simpler, more transparent models. But more transparent mass-balance models are open to the criticism that they are less generalizable and exclude potentially important elements. The challenge is to find ways to combine the transparency and ease of calibration of the simple fugacity-based mass-balance evaluation models with more complex activity tracking models.

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Table 1. OP pesticide usage in the Salinas Valley[a] and associated urinary DAP metabolites.

Pesticide[b]	Kilograms applied in 1999	Kilograms applied in 2000	Kilograms applied in 2001	Metabolites
Diazinon	47,847	56,883	60,699	DEP, DETP
Chlorpyrifos	29,423	27,325	24,975	DEP, DETP
Disulfoton	7,613	5,763	4,644	DEP, DETP, DEDTP
Total diethyls	84,883	89,971	90,318	
Malathion	35,188	45,727	43,873	DMP, DMTP, DMDTP
Oxydemeton-methyl	30,028	27,759	26,300	DMP, DMTP
Dimethoate	19,232	16,115	15,556	DMP, DMTP, DMDTP
Naled	11,979	9,315	7,748	DMP
Methidathion	6,779	6,926	6,464	DMP, DMTP, DMDTP
Phosmet	743	909	1,439	DMP, DMTP, DMDTP
Azinphos-methyl	626	101	56	DMP, DMTP, DMDTP
Methyl parathion	66	0	3	DMP, DMTP
Total dimethyls	104,640	106,852	101,439	

[a]Includes agricultural, landscape maintenance, structural pest control and roadside pesticide usage (DPR 1999, 2000, 2001).
[b]The approximately 48,000 kg of OP pesticides that do not metabolize to DAP compounds (e.g., bensulide, acephate, etc.) are not listed.

Table 2. Fugacity capacities in the ambient and indoor environment and overall persistence in the multiple media of the Salinas Valley environment.

Fugacity capacity (mol/m^3 per Pa)	Chlorpyrifos	Diazinon	Dimethoate	Malathion	Oxydemeton-methyl
Air	0.00054	0.00042	0.00042	0.00042	0.00042
Surface soil	120,000	120,000	25	52,000	350,000
Rooting-zone soil	120,000	120,000	25	52,000	350,000
Surface water	1000	87	100	2100	670,000
Vinyl floor	3.5×10^8	2.9×10^9	5.7×10^8	5.8×10^8	2.4×10^8
Carpet	1.0×10^7	6.9×10^7	1.6×10^7	1.6×10^7	7.3×10^6
Surface film	8,800	23,000	69	170,000	14,000
Dust	110,000	120	5.0	48,000	200,000
Overall persistence (Tov)	Chlorpyrifos	Diazinon	Dimethoate	Malathion	Oxydemeton-methyl
Salinas Valley environment	26 d	33 d	11 d	23 d	22 d
Indoor environment	> 1 y	> 1 y	> 1 y	> 1 y	> 1 y

Table 3. **Diethyl and Dimethyl OP Pesticides Intake (nmol) versus Output (nmol)**

(a) Diethyl OP Pesticides

Median Output: 22 nmol/day from CHAMACOS

12 nmol/day from NHANES

	Food intake nmol/d (based on national data)	CalTOX Inhalation estimate	CalTOX dermal	CalTOX non-dietary ingestion	
Chlorpyrifos	0.7 to 6	0.11	0.16	0.52	
Diazinon	0.1 to 8	1.4	0.49	7.2	**Total**
Total	0.8 to 14	1.5	0.65	7.7	11 to 22

(b) Dimethyl OP Pesticides

Median Output: 77 nmol/day from CHAMACOS

55 nmol/day from NHANES

	Food intake nmol/d (based on national data)	CalTOX Inhalation estimate	CalTOX dermal	CalTOX non-dietary ingestion	
Dimethoate	0.32 to 17	0.6	0.01	2.9	
Malathion	4 to 21	0.14	0.15	0.94	
Oxydemeton methyl	0.26 to 8.0	0.00059	0.0020	0.0043	**Total**
Total	5 to 46	0.74	0.16	3.8	8.8 to 51

Figure Titles

Figure 1. General scheme of the exposure assessment modeling. This mass balance diagram illustrates that the transfer of OP pesticides depends on the input rate and overall residence time (Tov) for these chemicals in the Salinas Valley region, the indoor environment, and the exposed individuals. For OP pesticides, these Tov values are respectively on the order of days, months, and days for region, house and person.

Figure 2. Estimates of environmental media fugacities (both ambient and indoor) for the Salinas Valley obtained from CalTOX and compared to measurements obtained from an intensive environmental sampling study of 20 farmworker families living in the region (Bradman et al. 2006).

Figure 3. Probability plot for the distributions of total diethyl and dimethyl DAP metabolite concentrations in the CHAMACOS cohort at their first prenatal visit (592 samples) and NHANES subjects who are female ages 18 to 40 (356 samples).

Figure 1.

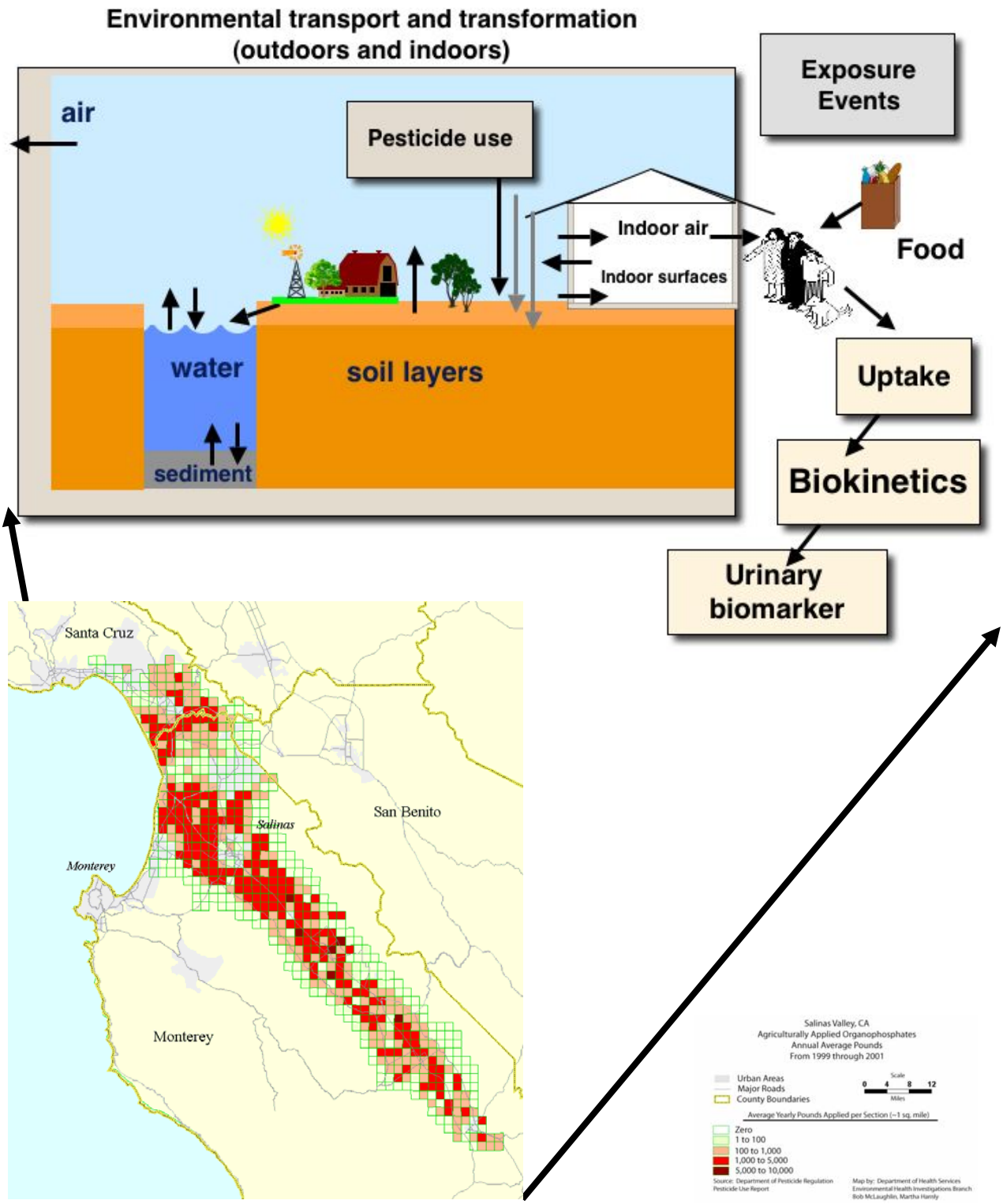

Environmental transport and transformation
(outdoors and indoors)
air
Pesticide use
Exposure Events
Indoor air
Indoor surfaces
Food
water
soil layers
sediment
Uptake
Biokinetics
Urinary biomarker
Santa Cruz
San Benito
Salinas
Monterey
Monterey
Salinas Valley, CA
Agriculturally Applied Organophosphates
Annual Average Pounds
From 1999 through 2001
Urban Areas
Major Roads
County Boundaries
Scale
0 4 8 12
Miles
Average Yearly Pounds Applied per Section (~1 sq. mile)
Zero
1 to 100
100 to 1,000
1,000 to 5,000
5,000 to 10,000
Source: Department of Pesticide Regulation
Pesticide Use Report
Map by: Department of Health Services
Environmental Health Investigations Branch
Bob McLaughlin, Martha Harnly

Figure 2.

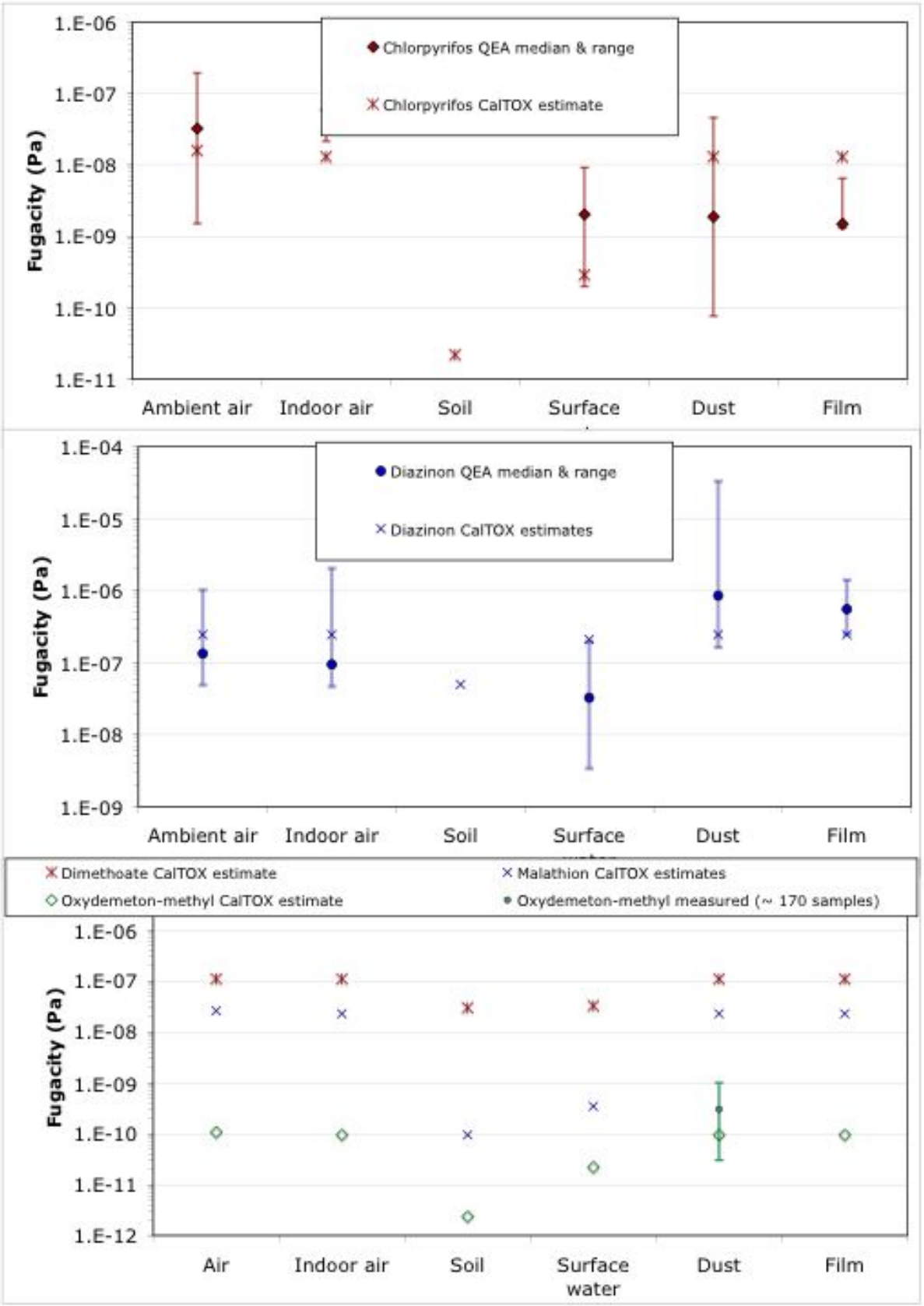
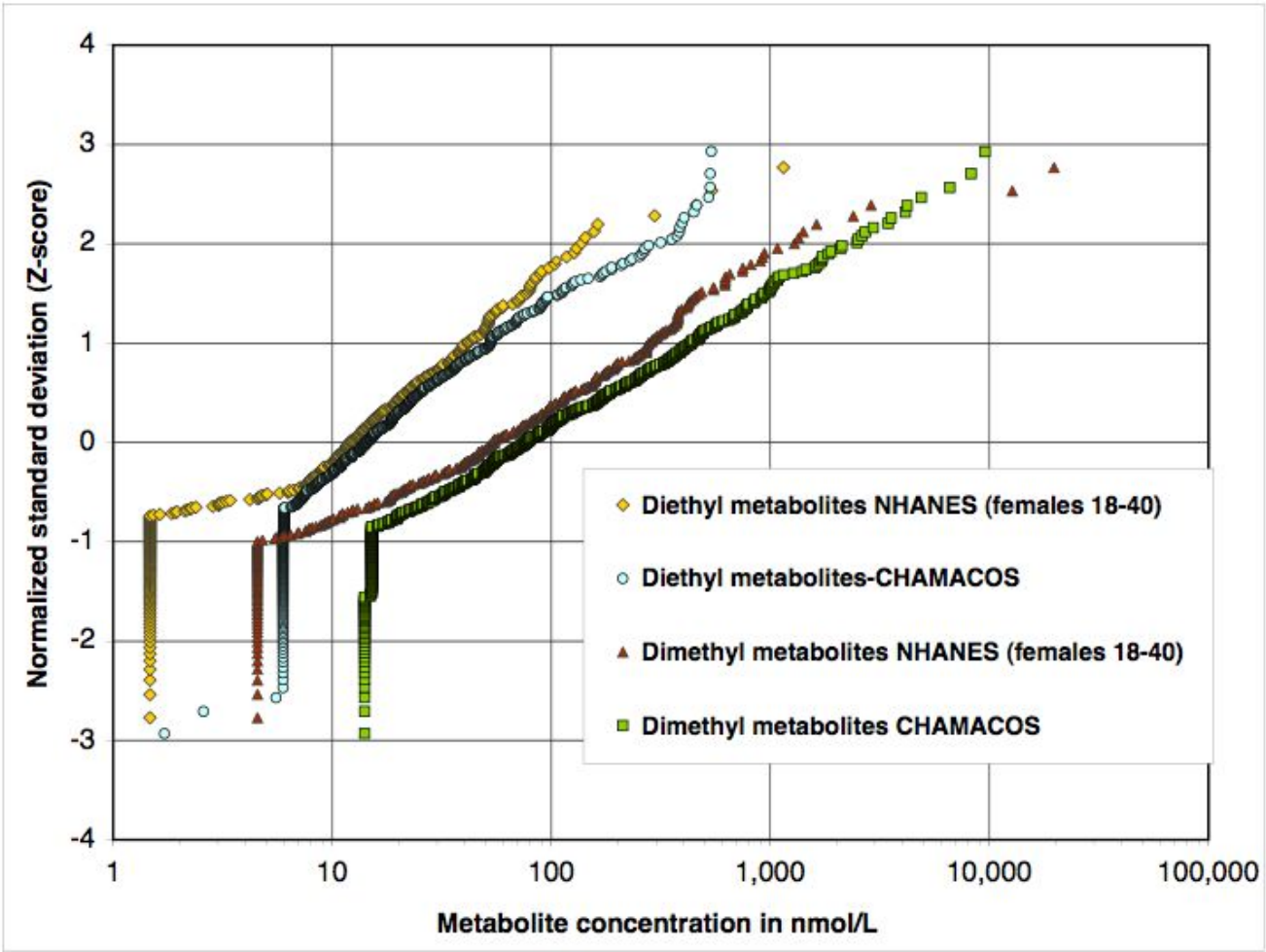

Chlorpyrifos QEA median & range
Chlorpyrifos CalTOX estimate
Fugacity (Pa)
1.E-06
1.E-07
1.E-08
1.E-09
1.E-10
1.E-11
Ambient air
Indoor air
Soil
Surface
Dust
Film
Diazinon QEA median & range
Diazinon CalTOX estimates
Fugacity (Pa)
1.E-04
1.E-05
1.E-06
1.E-07
1.E-08
1.E-09
Ambient air
Indoor air
Soil
Surface
Dust
Film
Dimethoate CalTOX estimate
Malathion CalTOX estimates
Oxydemeton-methyl CalTOX estimate
Oxydemeton-methyl measured (~ 170 samples)
Fugacity (Pa)
1.E-06
1.E-07
1.E-08
1.E-09
1.E-10
1.E-11
1.E-12
Air
Indoor air
Soil
Surface water
Dust
Film

Figure 3.


Normalized standard deviation (Z-score)
4
3
2
1
0
-1
-2
-3
-4
1
10
100
1,000
10,000
100,000
Metabolite concentration in nmol/L
Diethyl metabolites NHANES (females 18-40)
Diethyl metabolites-CHAMACOS
Dimethyl metabolites NHANES (females 18-40)
Dimethyl metabolites CHAMACOS